

Mayer G, Wang-Weigand S, et al. Efficacy and Safety of 6-month Nightly Ramelteon Administration in Adults with Chronic Primary Insomnia. Sleep 2009;32(3):351-360.

Design: Randomized clinical trial

Population/sample size/setting:

- 451 patients (166 men, 285 women, mean age 46) treated for primary insomnia in Europe, Russia, and Australia
- Eligible participants were over 18 years, BMI between 18 and 34, with at least 3 months of difficulty in initiating or maintaining sleep, self-reported total sleep time less than 6.5 hrs, self-reported sleep latency at least 4 min, and habitual bedtime between 10 PM and 1 AM
- Exclusion criteria were narcolepsy, parasomnias, sleep schedule change in past 3 months, alteration of exercise routine within 30 days, seizures, restless legs syndrome, fibromyalgia, periodic leg movement syndrome, psychiatric disorder, drug/alcohol abuse, or significant medical comorbid conditions
- In addition to self-reported criteria, all potential participants had 2 consecutive nights of polysomnography screening, with mean sleep latency of at least 20 minutes, apnea-hypopnea index less than 10 per hour, and periodic leg movements with arousal less than 10 per hour

Main outcome measures:

- All participants had a 2 week placebo run-in period, after which they were randomized to 8 mg ramelteon (n=227) or placebo (n=224)
- Participants were instructed to take ramelteon/placebo each night 30 minutes before bedtime for 6 months (168 consecutive nights)
- Main outcome measures were determined by polysomnography (PSG) during the first 2 nights of week 1 and the last 2 nights of months 1, 3, 5, and 6; latency to persistent sleep (LPS) was the primary endpoint, with total sleep time (TST) also assessed by PSG
- Several secondary measures were used; a digit symbol substitution test (DSST), memory recall tests, a VAS for mood and feeling, and a benzodiazepine withdrawal symptom questionnaire (BWSQ) were administered in the morning following waking from PSG
- PSG-measured LPS was about 70 minutes at baseline for each group; it decreased in both groups beginning with week 1 (approx. 45 min for placebo and 32 min for ramelteon); at subsequent measurements, there continued to be a shorter LPS with ramelteon (approx. 30 min) than with placebo (approx. 36 min)
- After 6 months, a 2 week placebo run-out period was conducted to evaluate whether rebound insomnia would occur; no rebound occurred, but placebo and ramelteon had equal LPS at the final PSG (approx. 38 min)
- TST was longer for ramelteon than placebo at week 1, but subsequent measurements did not show a difference between groups; both improved their TST from 329 min to 383 min for placebo and 373 for ramelteon

- Self-reported VAS symptoms (drowsiness, sedated, tired, sluggish, etc) did not differ between placebo and ramelteon during follow-up, nor were there measureable differences on DSST and memory testing
- BWSQ scores were also similar between groups

Authors' conclusions:

- Ramelteon 8 mg was well tolerated and significantly reduced sleep onset at all measured time points over 6 months compared with placebo
- There were no significant next-day residual effects, and there was no rebound insomnia or withdrawal symptoms

Comments:

- Although there were statistically significant differences in sleep onset between ramelteon and placebo, these differences were not reported in tabular form; they must be inferred from Figure 2, where they appear to be approximately 10 minutes or so
- Total sleep time was equal in the ramelteon and placebo groups
- The functional tests (DSST and memory) and the VAS scores effectively show that there was not a measureable blunting of mental acuity the day following PSG, there is no measureable improvement in task performance or wakefulness the following day
- The authors report that the mean percentage reduction in sleep latency was greater than 50% for ramelteon and less than 50% for placebo at all time points; however, this is not the same thing as comparing the proportion of participants with a 50% improvement in sleep latency
- The size of the study may lead to statistical significance where clinical importance is lacking for sleep latency
- The equality of total sleep time is robust, due to the large sample size
- The placebo lead-in time played an uncertain role; usually, these are done in order to exclude non-compliant participants from being randomized, but the numbers of exclusions for this reason (or the criteria for exclusion for non-compliance) are not certain

Assessment: Adequate for evidence that ramelteon has no effect on total sleep time, and only a small reduction in sleep latency, with no measureable effect on daytime function